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EXAMINER

KERR, KATHLEEN M

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 03/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/509,608

Applicant(s)

WEBER ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/3/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-53 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Application Status

1. In response to the previous Office action, a final rejection (Paper No. 12, mailed on July 2, 2002), Applicants filed an after-final amendment received on November 4, 2002 (Paper No. 14), which was not entered per Advisory Action, Paper No. 15 mailed on December 3, 2002. Applicants then filed a request for continued examination (RCE) on February 3, 2002 requesting the entry of the amendment filed on November 4, 2002 (Paper No. 14). Said amendment amended the Abstract and Claims 27, 36-39, 42-44, and 53. Thus, Claims 27-53 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for International Application No. PCT/EP98/06134 filed on September 28, 1998. The instant application is also granted the benefit of German application 197 44 212.9 filed on September 30, 1997 in the absence of a translation since no intervening art has been identified.

Drawings

3. As previously noted, the drawings filed on April 22, 2002 have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Maintained - Objections to the Specification

4. Previous objection to the specification for lacking an adequately descriptive Abstract is maintained. Applicants amended the Abstract; however, the completeness of the Abstract is

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wholly inadequate. It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. In the instant case, the Abstract does not even mention the types of enzymes used; it wholly lacks any specific description of the disclosed subject matter. The Examiner suggests the inclusion of the enzyme names, in full and their abbreviations, for completeness.

Withdrawn - Claim Objections

5. Previous objection to Claim 36 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicants' amendment.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

6. Previous rejection of Claim 32 and 37-42 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms "t-HMG gene" and "SAT1" is withdrawn by virtue of the Examiner's reconsideration since the instant claims particularly define the plasmid structure used. In Examples 1 and 2, using specific sequence primers, plasmids YEpH2, YDpUHK2, and pADL-SAT1 are produced. Thus, these primers define the genes in the plasmids making the instant claims clear.

7. Previous rejection of Claims 27-35 and 52 under 35 U.S.C. § 112, second paragraph, as being indefinite for how the claimed method produces one or more intermediate products of ergosterol biosynthesis is withdrawn by virtue of Applicants' amendment.

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8. Previous rejection of Claims 37-42 under 35 U.S.C. § 112, second paragraph, as being indefinite because the composition of the plasmids noted in the claims is drawn to *any* ADH promoter, *any* t-HMG gene, *any* TRP-terminator, *any* kanamycin resistance gene, *any* ura3 gene, and *any* SAT1 gene is withdrawn by virtue of Applicants' amendments to the claims.

9. Previous rejection of Claim 42 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "a sterol with a 5,7-diene structure" is withdrawn by virtue of Applicants' amendment.

10. Previous rejection of Claims 43, 44, and 46-51 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "flanked" is withdrawn by virtue of Applicants' amendment.

Maintained - Claim Rejections - 35 U.S.C. § 112

11. Claims 27-29, 32-35, and 51-53 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "intermediate products" is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that "intermediate products" are well known in the art to mean "a molecular species that is formed from reactants and which further reacts to form the products of the reaction". The Examiner does not disagree. However, this definition does not define the term in the claims since the reactions are also not specified. Applicants also cite a dictionary definition of the term; however, without clear metes and bounds of the reactions encompassed, the intermediate products intended in the claim are unclear as to their metes and bounds. As previously noted,

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“It is unclear where the metes and bounds of ergosterol biosynthesis lie. Biosynthesis and metabolism in organisms are complex, intertwined processes. Without clear definition of what compounds are encompassed by the term “intermediate products”, one could argue that glucose was an intermediate product since it is involved in most biosynthetic processes. The metes and bounds of the claims must be clearly defined so that one of skill in the art understands exactly where the patent coverage begins and ends. Appropriate correction is required.”

12. Previous rejection of Claims 27-31, 33-36, and 43-53 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms “t-HMG gene” and “SAT1” is maintained.

Applicants’ arguments have been fully considered but are not deemed persuasive.

Applicants argue that “tHMG” is clearly an altered form of HMG1 taught by Basson *et al.* as mentioned in the specification on page 7. No description of the alteration is set forth in the specification on page 7; the description here simply states “altered variant of HMG1”.

Additionally, the description on page 9 is wholly inadequate to clearly describe the alteration of HMG1 to produce tHMG since no mention of tHMG is found on page 9 and no particular description of the alteration (i.e., what are the membrane-bound domains and the catalytic domains) is disclosed. Thus, the particular make-up of tHMG is wholly unclear.

Applicants argue that “ARE1...corresponds to SAT1”; the Examiner is unclear as to what “corresponds to” means? Is ARE1 equivalent to SAT1? Moreover, how does this clarify what the nature of SAT1 is? Clarification is required for both terms.

The Examiner suggests a reference to the primers used to clone tHMG and SAT1 in Examples 1 and 2, respectively, to clearly define the instant genes. Said reference could be added to the end of the instant claims in the form of a ---wherein--- clause.

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13. Previous rejection of Claim 53 under 35 U.S.C. § 112, second paragraph, as being incomplete because it omits essential steps of producing ergosterol as required by the preamble is maintained. Applicants amend the claim to include of step of isolating the “expressed ergosterol of intermediate products”; however, this step is unclear since the term ---expression---is reserved for genes. The Examiner suggests replacing the phrase being with the term “isolated” with step c from Claim 27. Appropriate correction is required.

14. Previous rejection of Claims 27-31, 33-36, and 43-53 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the specification need not present the invention in *ipsis verbis*, that the citations on pages 2-3 of the specification are sufficient. On page 2, a single example of each of the following yeast genes is described: HMG-CoA reductase, squalene synthetase, acyl-CoA:sterol-acyl transferase, and squalene oxidase all from *S. cerevisiae*. The instant methods and products are adequately described for this limited scope, using these particularly named genes. However, the instant methods are *much* broader in scope, being methods using ANY HMG-CoA reductase from ANY organism, ANY squalene synthetase from ANY organism, and so on. Limited examples of these enzymes, particularly from other organisms, are found in the art. Without adequate description of the structure of the genus of HMG-CoA reductases, squalene synthetases, and so on, the single example provided does not adequately describe the genus such that one of ordinary skill in the art would be able to predict the structure of other members of the claimed genus.

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15. Claims 32 and 37-42 are rejected under 35 U.S.C. § 112, first paragraph, enabling deposit, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that the deposit of the plasmids is unnecessary because they can be produced, as described in the specification, using publicly available materials. The Examiner disagrees for the following reasons.

Plasmid YEpH2 (see Example 1 in the instant specification) requires the use of tHMG cloned using primers (SEQ ID NOs: 1 and 2, enabled), pUC19 (commercially available and enabled), pPT26 (Lang and Looman, 1995), and YEp13 (Fischhoff *et al.*, 1984); no evidence of the commercial availability of pPT26 or YEp13 is provided.

Plasmid YDpUHK3 (see Example 1 in the instant specification) requires the use of YEpH2 (so all of the above) and YDpU (Berben *et al.*, 1991); no evidence of the commercial availability of pPT26, YEp13, or YDpU is provided.

Plasmid pADL-SAT1 (see Example 2 in the instant specification) requires the use of SAT1 cloned using primers (SEQ ID NOs: 3 and 4, enabled), pGEM-T (Mezei and Storts, 1994), pADH1001 (unknown source), and YEp13 (unknown source); no evidence of the commercial availability of pGEM-T, pADH1001 or YEp13 is provided. Moreover, the particular fragment of YEp13 containing the LEU2 gene is not disclosed so its exact nature could not be reproduced without undue experimentation.

Thus, by Applicants arguments, to enable plasmids YEpH2 and YDpUHK3 without Applicants' deposit, a showing of the public availability of pPT26, YEp13, and YDpU is required. To enable plasmid pADL-SAT1 without Applicants' deposit, a showing of the public availability of pGEM-T, pADH1001 and YEp13 is required as well as a better description of the

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LEU2 fragment of YEp13 such that pADL-SAT1 can be exactly duplicated and, thus, be in the hands of the public without undue experimentation.

Alternatively, to enable the instant claims by enabling the deposit of YepH2, YDpUHK3, and pADL-SAT1 plasmids, the following items are required: (1) the accession number assigned by the depository, (2) the date of deposit, (3) a brief description of the deposit, (4) the name and full address of the depository (37 C.F.R. § 1.801 - 1.809) (those which are in bold have not been fulfilled by the instant specification), and (5) the record must also contain a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent (see M.P.E.P. § 2404.01); this statement may be certified by Applicants or Applicants' representative

Withdrawn - Claim Rejections - 35 U.S.C. § 102

16. Previous rejection of Claim 53 under 35 U.S.C. § 102(b) as being anticipated by Saunders *et al.* is withdrawn by virtue of Applicants' amendment deleting the scope of the claim taught by Saunders *et al.*

NEW ISSUES

Claim Objections

17. Claim 45 is objected to for a typographical error. In item c, the "ADP-promoter" should be an ---ADH-promoter---as found elsewhere in the claim and throughout the specification.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claim 29 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27, on which Claim 29 depends, is drawn to methods using a single multi-gene plasmid (i-vi) or two more single gene plasmids (vii). The requirement in Claim 29 of independently introducing plasmids is only clear with respect to item vii, and not with respect to items i-vi. Clarification is required.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claim 53 is rejected under 35 U.S.C. § 102(b) as being anticipated by Jennings *et al.* (see IDS). The instant claim is drawn to a method of producing intermediate ergosterol products using a microorganism expressing ERG9.

Jennings *et al.* teach the expression of ERG9 in *E. coli* and an assay of the encoded squalene synthetase activity using gas chromatography, which procedure inherently isolated ergosterol intermediates, particularly presqualene diphosphate, the product of the synthetase reaction.

Summary of Pending Issues

20. The following is a summary of the issues pending in the instant application; all issues must be addressed in a complete response to the instant Office action.

- a) The specification stands objected to for lacking an adequately descriptive Abstract.
- b) Claim 45 stands objected to for a typographical error.
- c) Claims 27-29, 32-35, and 51-53 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “intermediate products”.
- d) Claims 27-31, 33-36, and 43-53 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms “t-HMG gene” and “SAT1”.
- e) Claim 29 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for being confusing.
- f) Claim 53 stands rejected under 35 U.S.C. § 112, second paragraph, as being incomplete because it omits essential steps of producing ergosterol as required by the preamble.
- g) Claims 27-31, 33-36, and 43-53 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
- h) Claims 32 and 37-42 stand rejected under 35 U.S.C. § 112, first paragraph, enabling deposit.
- i) Claim 53 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Jennings *et al.*

Examiner's Suggestions

21. The following are not rejections, but are the Examiner's suggestions for more suitable claim language to better align the instant claim language with terms of art. While the instant

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claim language meets the statutory threshold of clarity and precision, a more suitable expression of the claimed subject matter is suggested. Such suggestions are encouraged in M.P.E.P. § 2173.02.

- a) In Claim 27, item c, the Examiner suggests producing ---ergosterol and/or one or more intermediate products of ergosterol biosynthesis--- to better match the preamble of the claim and to not limit the claim unnecessarily to producing both ergosterol and ergosterol precursors.
- b) In Claim 52, items d and e, the Examiner suggests extracting and purifying ---ergosterol **and/or** its intermediate products---.

Additional Art of Record

22. The following reference is cited to complete the record; it is not used in an art rejection of record presently:

- a) Lees *et al.* Biochemistry and molecular biology of sterol synthesis in *Saccharomyces cerevisiae*. Biochem. Funct. Sterols (1997) 85-99. Editor(s): Parish *et al.* Publisher: CRC, Boca Raton, Fla.

Conclusion

23. Claims 27-53 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229.

The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read "Kathleen M. Kerr". The signature is fluid and cursive, with the first name "Kathleen" and last name "Kerr" clearly distinguishable.

KMK

March 17, 2003